From Bench to Battlefield: The Neuroscience of Combat Stress Risk and Resilience

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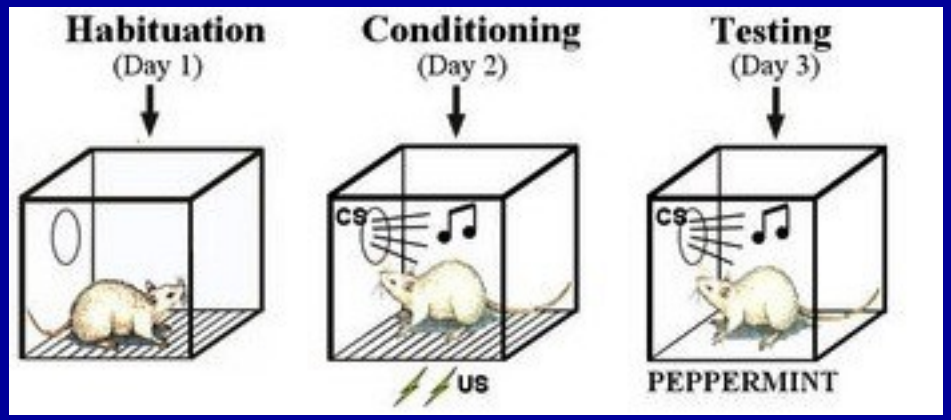
Objectives

- Describe how neuroscience research methods help us better define combat stress
  - Risk
  - Resilience
- Translate neuroscience research methods into clinical practice/ operations.

What is “normal” stress response?

- OIF/OEF PTSD risk is 1 in 5.
- A monozygotic twin makes risk 1 in 3.
- Civilian research focused on illness risk
- We need to better understand:
  - Resistance: same stress exposure, no illness
  - Resilience: faster recovery from illness
- What can neurobiology of fear tell us?

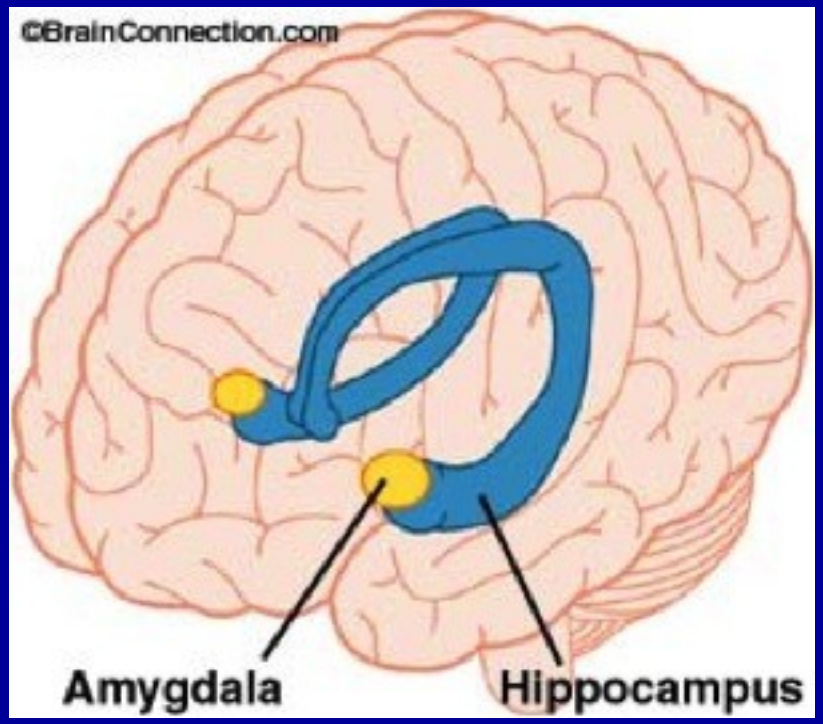
Biobehavioral model of fear



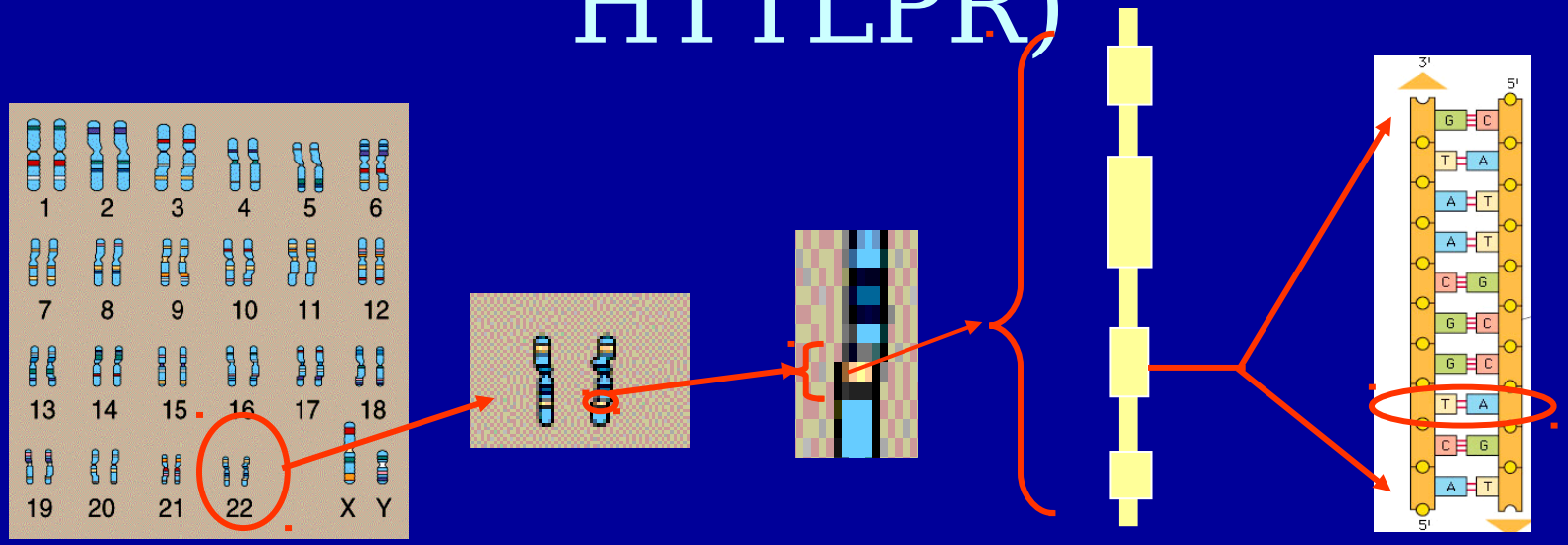
- PTSD thought of in terms of Pavlovian conditioning:
  - An over-reaction to threat cue.
  - This model used to develop new drug trials.
  - Yet, only one of six PTSD studies support this model.
  - Why so much variance in PTSD fear learning ability?

Neurobiology of Fear

- Conditioned fear ability associated with amygdala brain region
- Amygdala activity regulated in part by serotonin neurotransmitter.
- Serotonin affects depression and anxiety.



Serotonin Transporter Promoter Variant (5-HTTLPR)



genome

Pair of Chromosomes (2 Strands of DNA each)

locus

gene

site

- Common polymorphism in promoter region regulates gene expression
- Genotypes: l/l or l/s or s/s
- Long variant = increased serotonin “RESILIENCE”

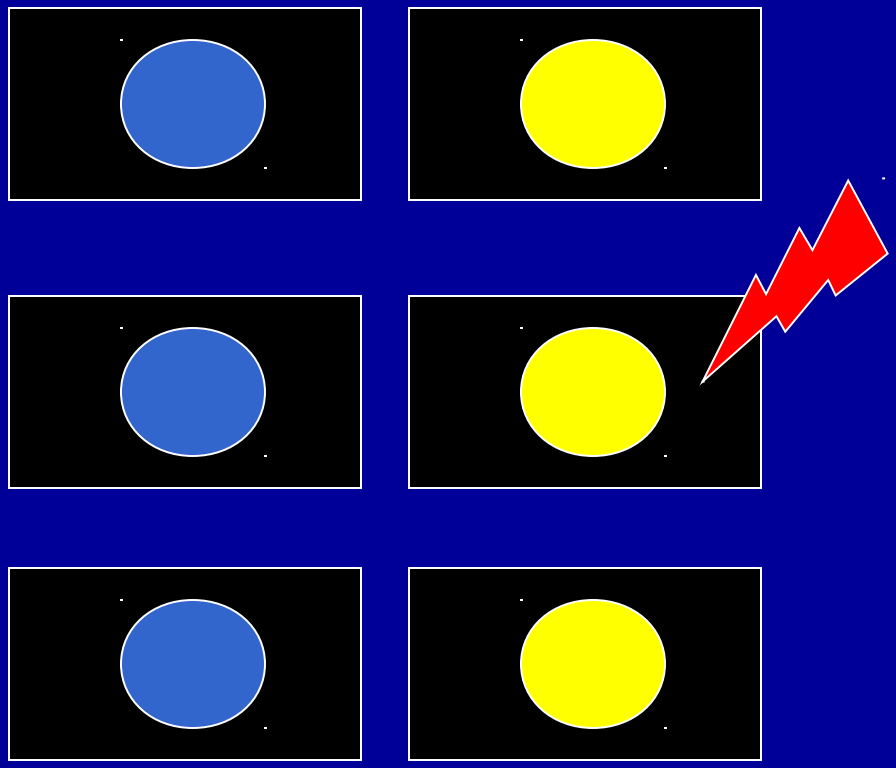
Current Study

- Investigate ability to learn fear and safety cues
- Compare PTSD and Stress Resistant Service Members
- Study brain activity during fear learning
- Categorize Service Members by Serotonin risk and resilience gene variants.

Participants

- 10th Mountain Division (LI).
  - Right handed, medication-free, metal-free.
- Active Duty Male Service Members:
  - PTSD (n=14).
  - Combat Resilient (n=14).
  - Pre-Deployed (n=15).

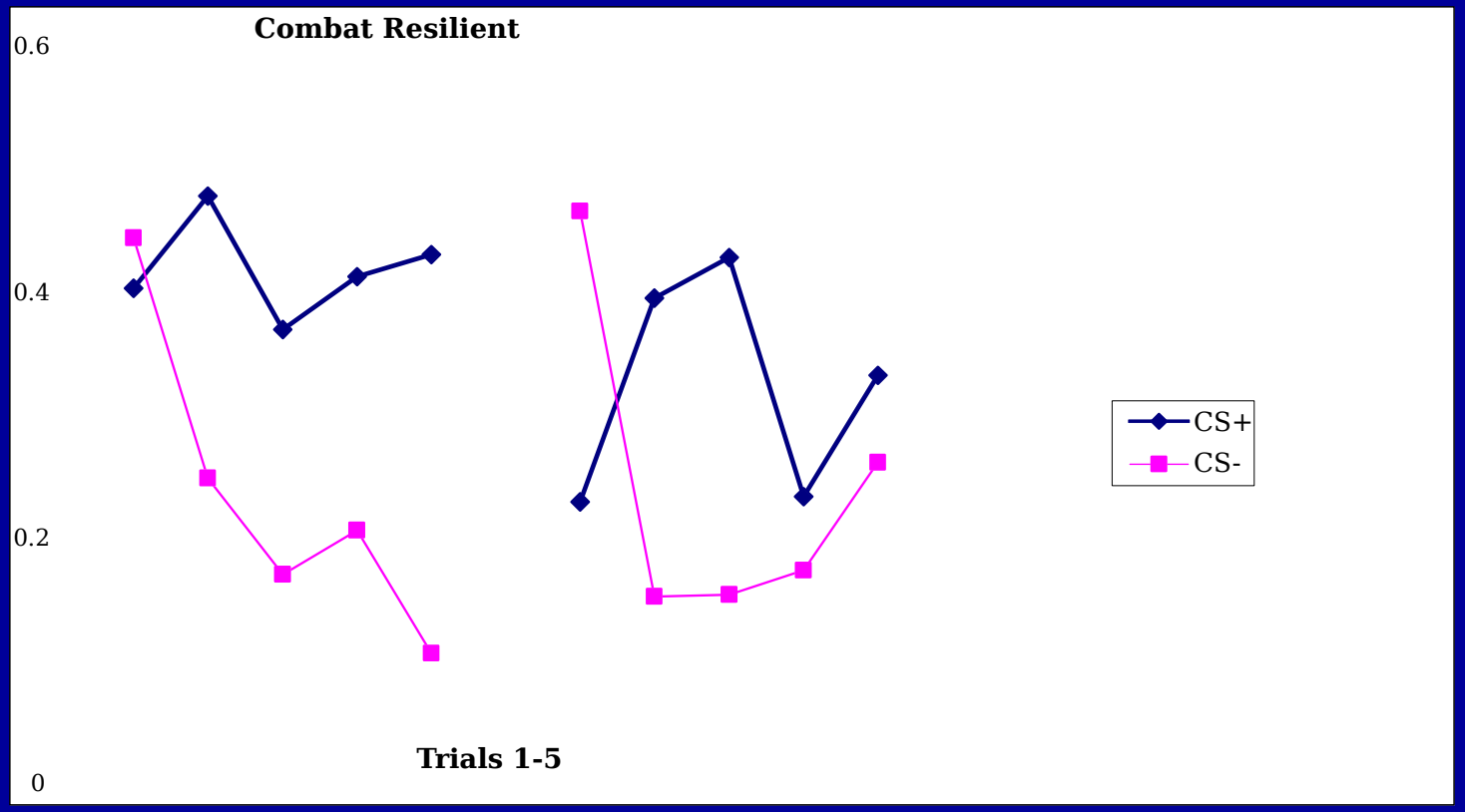
Research Procedure



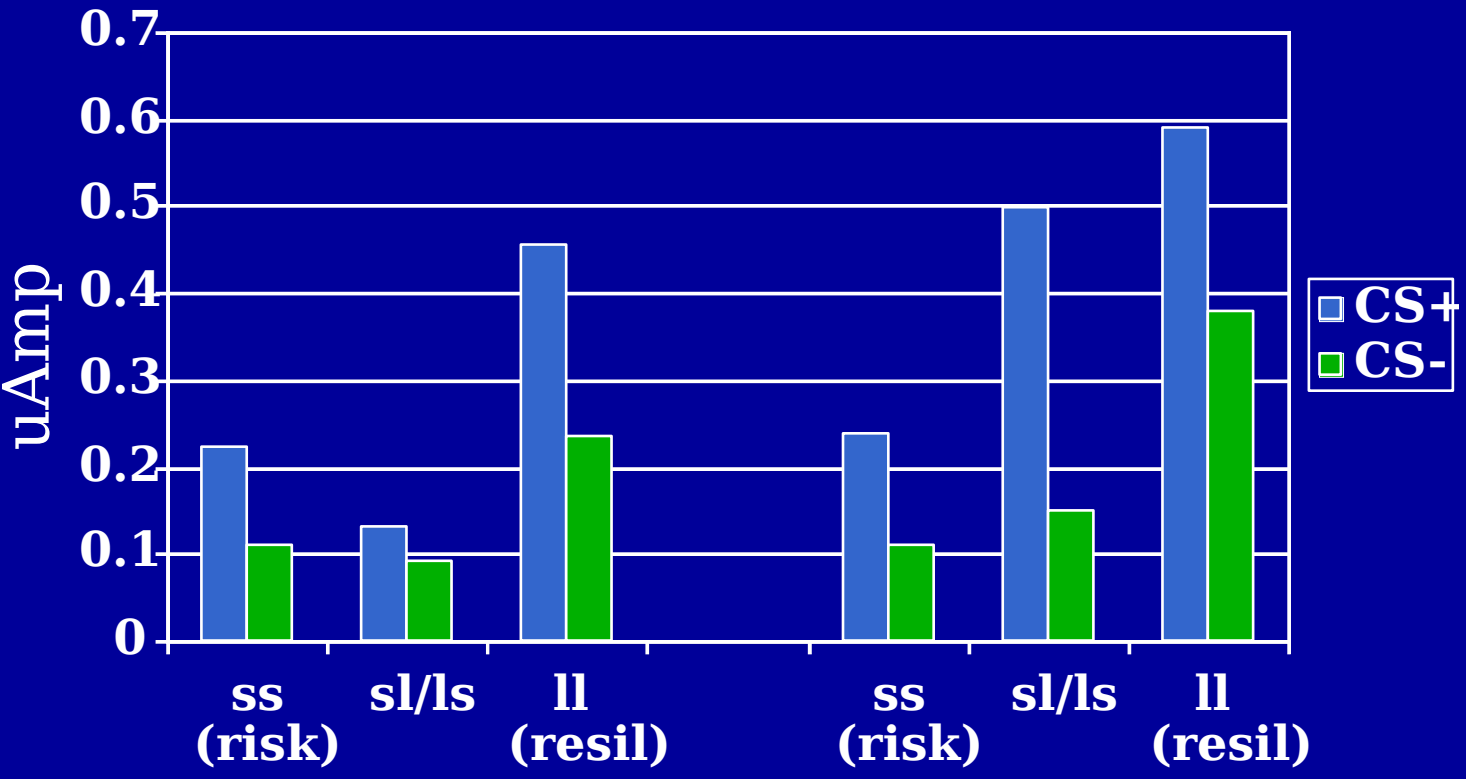
Demographics

	PTSD	Stress Resistant
Age	24 (3)	24 (3)
Education	12 (1)	13 (1)
Yrs. Service	4 (3)	5 (2)
CES	30 (7)	27 (6)
CAPS	66 (4)	16 (4)

Identifying Threat (CS+) from Safety (CS-)



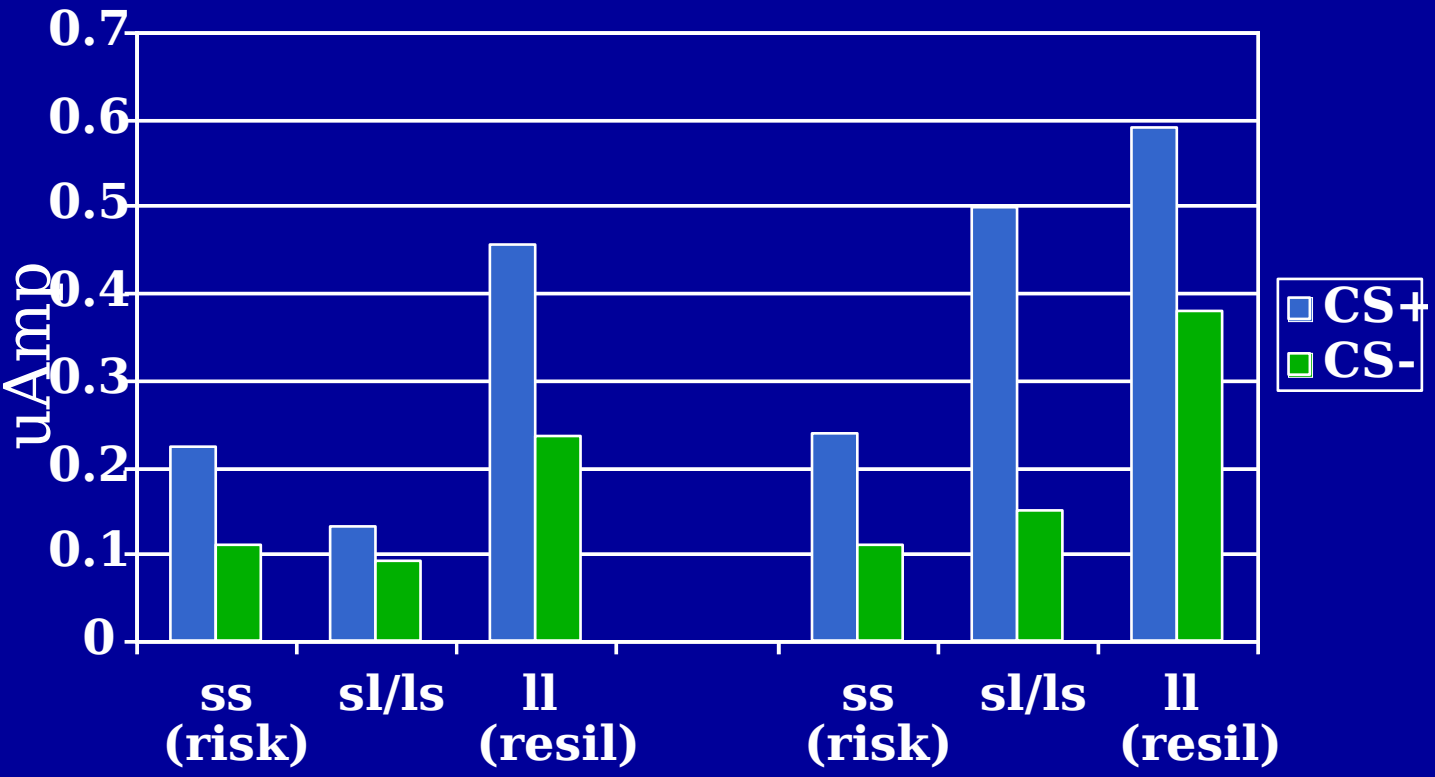
The ability to discriminate threat from safety varies by 5HT2C polymorphism



PTSD

Stress Resistant

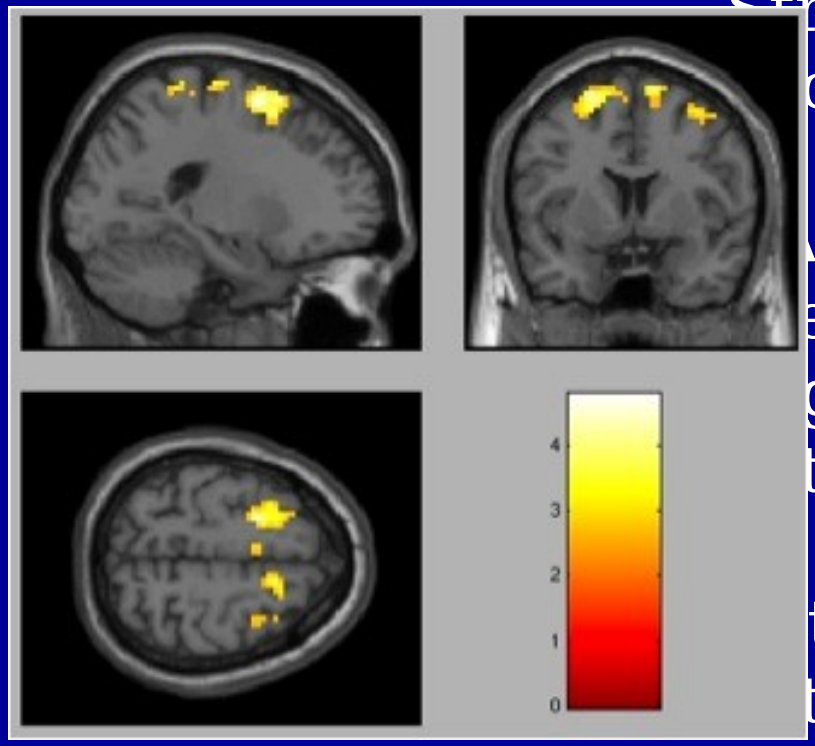
The ability to discriminate threat from safety varies by 5HT2C polymorphism



oat Stress	28	30	28	26	28	30
D severity	64	74	56	5	22	6

PTSD Stress Resistant

fMRI Results: Stress Resistant



tress Resistant Service Membe
ow greater CR+ in Lateral BA

6 is defined as a pre-motor
ea, often found active during
gnitive tasks to prepare for
tion.

tivity motor areas may inhibit
tivity in fear network.

Summary: PTSD

- No support for “over reaction” model.
  - Over time, a “general alarm”
- “Risk” gene associated increased PTSD severity and poor ability to identify threat from safety signals.

Summary: Stress Resistance

- Stress Resistant Service Members not “fearless”.
- Make good use of threat and safety cues.
  - Conditioned fear response engages brain areas for motor output planning.
  - Likely prevents fear circuit from over-reacting.
- Provide building blocks for operational functioning.

Translation to Clinical Value

- In separate pilot study:
  - Veterans with strong conditioned response responded very well to 8 wk SNRI treatment (Duloxetine).
  - Veterans with weak/no conditioned response saw no improvement.
- Conditioned Fear provides marker for treatment.
- Need to change models for treatment.
- Can we screen for stress resistant Service Members?

Research Team

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